Multi-regional Clinical Trials – Considerations in Design and Analysis

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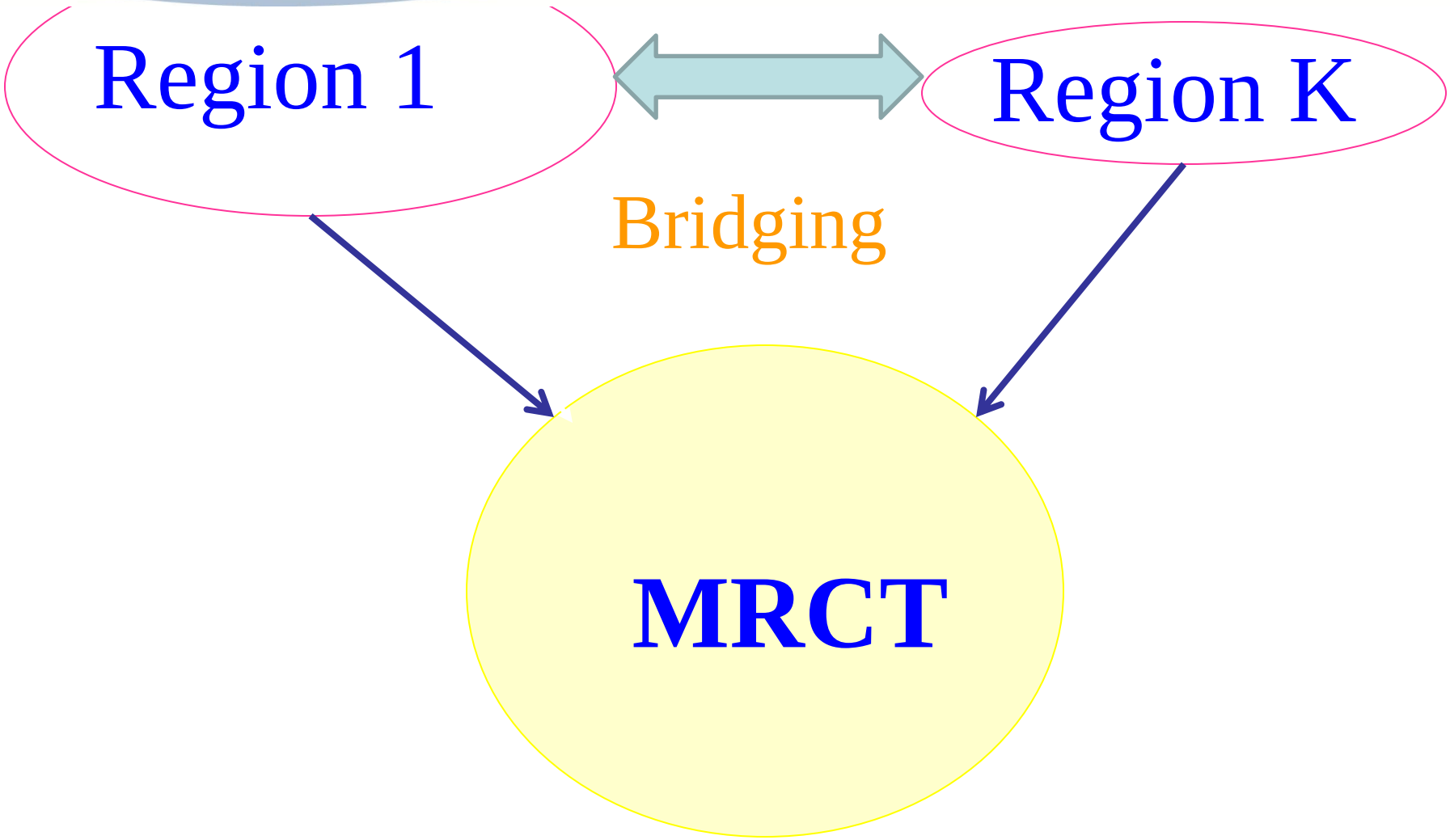
Outline

- The Science of MRCT
  - Basic concepts
  - Issues in Efficacy and Safety
  - Some Design and Analysis considerations
- Training Initiatives by FDA
  - APEC CoE MRCT training
- Collaborative Initiatives by FDA
  - International initiatives in Mini-Sentinel
- Concluding Remarks


Region 1
Region K
Bridging
MRCT

Multi-regional Clinical Trials (MRCT)

- 65% of all trials reviewed by CDER are MRCTs according to an unofficial survey
- The basic tenets are laid out in ICH E5 – Ethnic Factors in the Acceptability of Foreign Clinical Data (www.ich.org)
  - The Q&A section is especially helpful

ICH E5 - Ethnic Factors in Acceptability of Foreign Clinical Data

- Assessment for acceptability of foreign data
- Extrapolation to new region and new studies
- Bridging Data Package
  - Definition
  - Nature and Extent
  - Bridging studies for Efficacy and Safety
- Developmental Strategies for Global Development
- A companion Q&A guidance gives lot more detail and clarification

Sources of differences(1)

- The regional differences in drug effect are primarily from two sources
- intrinsic factors race, genetic factors, …
- extrinsic factors background treatment, social factors, health care system, medical practices, …
- quality of trial conduct or data

Sources of Differences (2)

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- The regional differences of real interest, if any, are those attributed to intrinsic and extrinsic factors (ethnic or genetic differences, medical practices and health care systems etc.)
- Data/trial conduct quality problem can accentuate or attenuate regional differences in treatment effect in terms of effect estimate, but it will increase variance of the global estimate

Design Consideration

Are key endpoints culturally sensitive? (particularly soft endpoints)

- If so, MRCT may not be a good option

Define geographical region(s) in a broader sense

- Multiple definitions may be needed
- Consider defining it based on intrinsic & extrinsic factors

Design Issues

- Is overall treatment effect meaningful, or interpretable for all regions?
- If not, it is only applicable to a particular region.
  - The study will require a sufficient sample size for that region
    - Overall treatment effect is a weighted mean

Concept of quality

- Implement quality measure in each region

-Explore a possible need of more conservative sample size planning

- Need prior experiences

- Global estimate is still the key

- Discuss extent of acceptable regional differences

Analysis Consideration

- Regional estimates
  - Report regional estimates of treatment effect
  - Explore consistency/inconsistency of regional estimates
  - If there is a large inconsistency, explore possible differences
    - baseline characteristics? background medications? intrinsic/extrinsic factors? data quality?

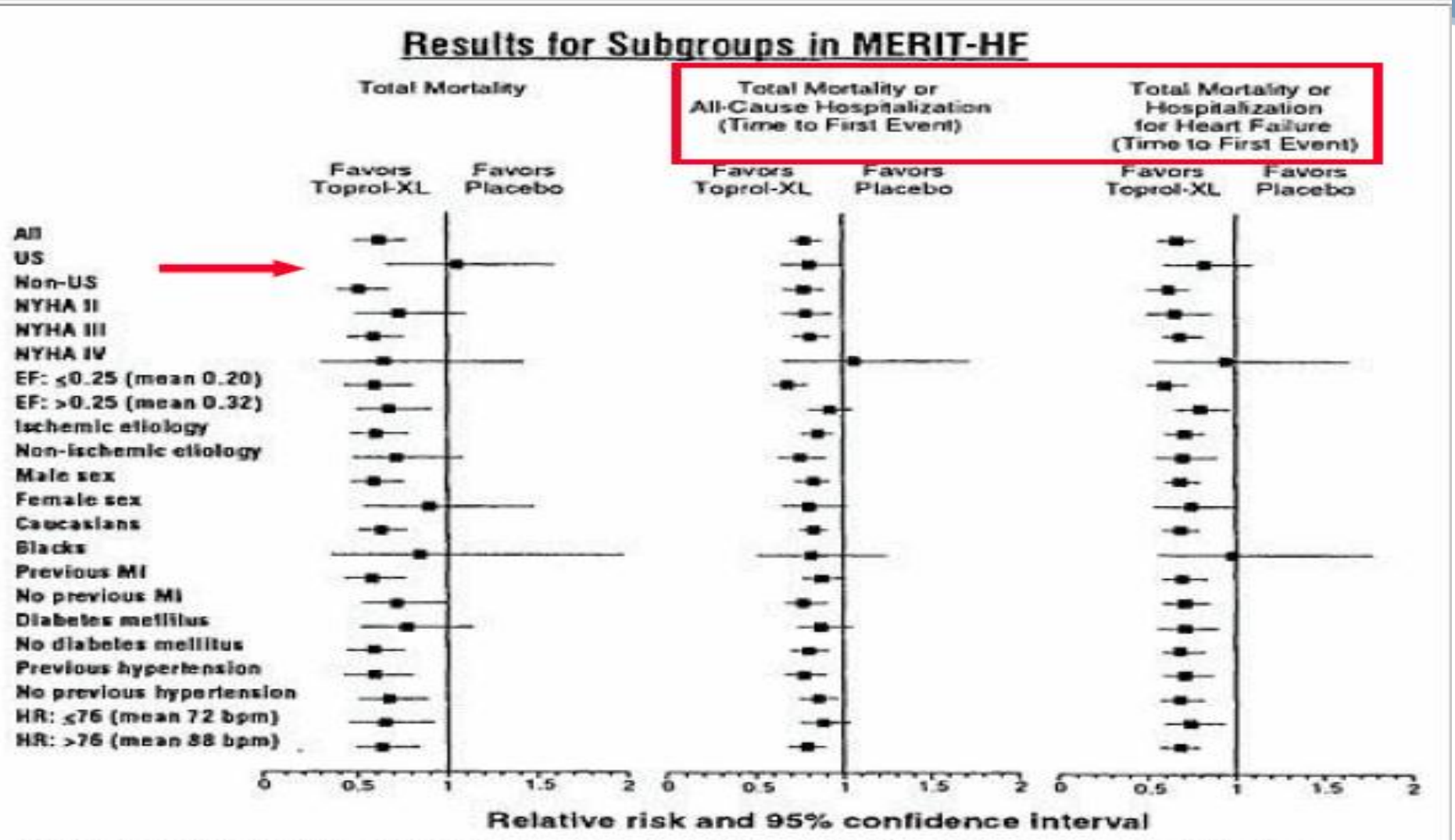
Graphical Tools

- Funnel plot
  - effect size estimate vs. N (or number of events)
- Forest plot
- P*hyp* plot*
  - p-value & p-value quantile curve vs. sample or number of events, given the treatment effect
- Galbraith plot: Odds-ration with standard error

*Hung, O'Neill, Bauer, Köhne (1997, Biometrics)

#Galbraith et al (1988, Stat. in Med.)

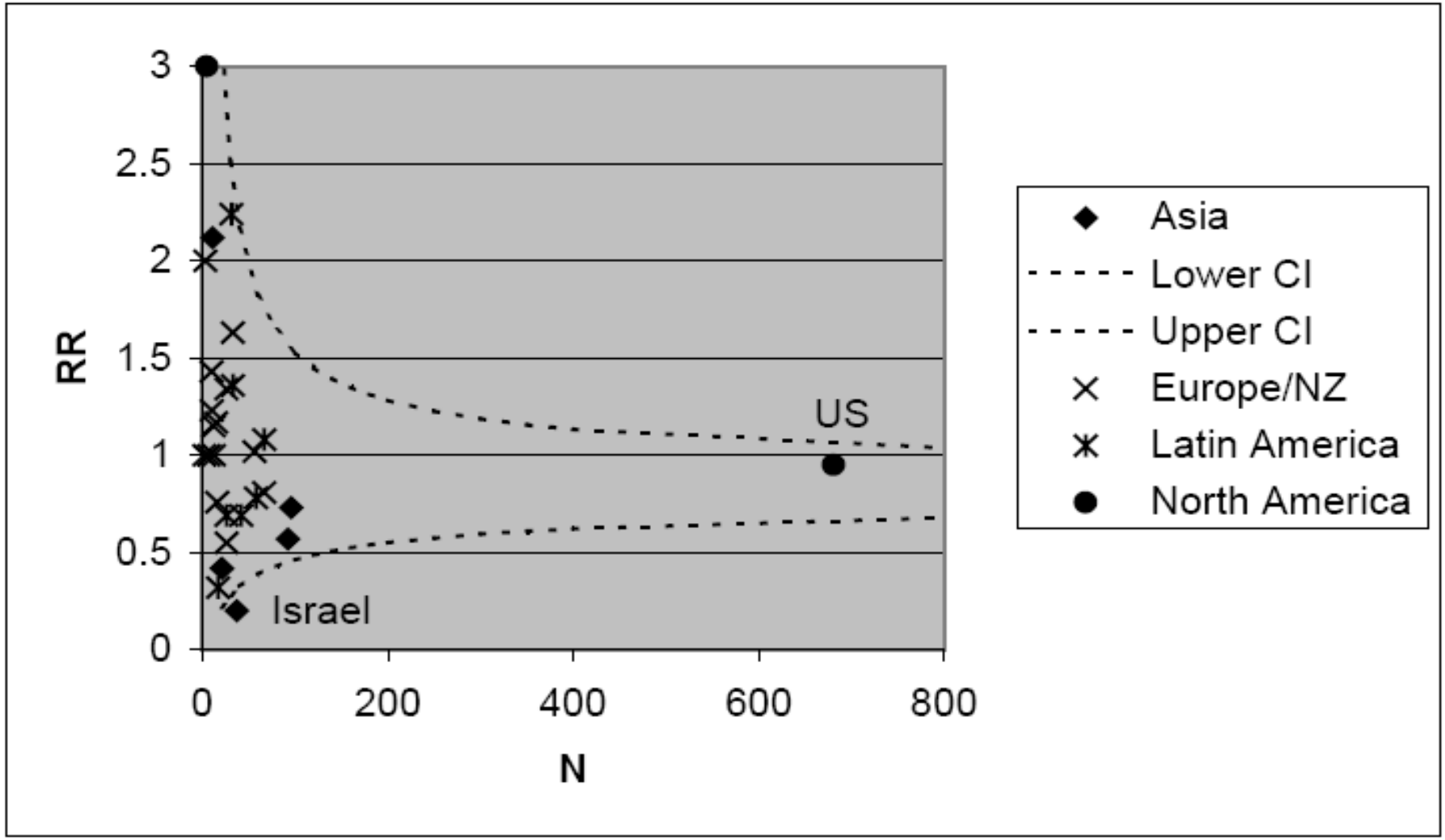
Forest plot of subgroups



From drug label. O'Neill (2007)

Funnel Plot of RR by country

Figure 7. Relative Risk of Primary Composite Endpoint by Country.



Descriptive measures of inconsistency

- Probability of reversal (pt est < 0 vs > 0)
  - K regions
  - Total sample size N planned to detect a drug effect δ (standardized) > 0 at level α, and power 1-β
  - Sample size for region *h* : λ_hN

    (assuming equal allocation for treatments): assume equal variance among regions
- Testing treatment by region interaction
- Testing qualitative interaction **Gail & Simon, 1985, Biometrics**

Global trials yielding an overall +ve treatment effect

P-value	Prob one region shows reversal	Prob two regions show reversals
.001	0.17	0.01
.01	0.29	0.05
.05	0.38	0.11

4 regions equal allocation

P-value	Prob one region shows reversal	Probability two regions show reversals
.001	0.23	0.02
.01	0.33	0.06
.05	0.40	0.13

4 regions (0.2, 0.1, 0.3, 0.4)

True effect close to observed effect

MRCT Training Initiatives

- Wide audience targeted– DIA, ICSA, ASA
- Train International Regulators
  - CDER Forum: a week long program, bi-annually
  - APEC MRCT CoE Pilot
- Focus on basic tenets of regulatory science and its quantitative framework
  - Evidentiary standard
  - Data requirements and standards

APEC MRCT CoE Pilot (1)

- APEC = Asia-Pacific Economic Co-operation
  - 21 member countries
  - Emerging market, emerging patient base in RCTs
  - Unique bridging requirements – often of inadequate sizes to draw valid region-specific conclusions
- Center of Excellence to provide continuing education, support and consistency
  - Pilot co-sponsored by National University of Singapore (NUS), HSA and Duke University

APEC MRCT CoE Pilot (2)

- Faculty = Industry + Academia + Regulators
- Three-day hands-on sessions: each participant mentored by a faculty in a multi-country team
  - *Protocol design: pre-defined geographical regions and how to account for differences in epidemiology and medical practice (extrinsic factor)*
  - *Statistical analysis plan: statistical significance versus clinical trend analysis when evaluating clinical efficacy in sub-populations .*

APEC MRCT CoE Pilot (3)

- Finding the Right Dose; Consideration of Dosing in Asian Patients
- Safety: Safety signal detection, clinically meaningful events - confounding factors, risk-benefit evaluation.
- Economy-Specific Requirements To Satisfy Registration: Bridging Studies and Beyond
- Mock submission by Industry

Sentinel Initiative

- Develop an active electronic safety monitoring system to
  - Active Surveillance System
  - Strengthen FDA's ability to monitor post-market performance of medical products
  - Augment, not replace, existing safety monitoring systems
  - Enable FDA to access existing automated healthcare data by partnering with data holders (e.g., insurance companies with large claims databases, owners of electronic health records, others)

Sentinel – International Efforts

- **Europe**
  - **European Network of Centers for Pharmaco-epidemiology and Pharmaco-vigilance (ENCePP)**
    - Create a "network of excellence" consisting of research and medical-care centers, healthcare databases, electronic registries and existing networks to strengthen post-marketing monitoring to facilitate the conduct of safety related post-approval studies
  - **IMI/PROTECT**
    - To develop and validate tools and methods that will enhance AE data collection, active signal detection, create standards for pharmaco-epidemiology studies, and means to integrate all data know about a product for evaluation of risk : benefit
  - **EU-ADR**
    - Design, develop and validate a computerized system that exploits data from electronic healthcare records and biomedical databases for the *early detection of adverse drug reactions;* complementary to existing systems, have more power and detect signals earlier

Sentinel – International Efforts (2)

- **Canada**
  - **Drug Safety and Effectiveness Network (DSEN)**
    - Enable research by linking researchers through a new virtual network, creating a national agenda of research based on priorities identified by decision-makers, provide funding for research to assess the risks and benefits of drug products that are on the market.
- **Japan**
  - **Utilization of Electronic Medical Records (EMR) and Claims Data in Pharmacovigilance**
    - Secure access to EMR database including claim data to assess drug safety through ADR incidence survey and using a pharmacopeia approach

Concluding Remarks

- MRCTs are a real part of our reviews: complex, challenging and rewarding
- Careful attention to planning
- Training and collaboration important
- Global harmonization and regulatory leadership - critical

Acknowledgements:
Hsien-Ming Jim Hung
Lisa LaVange